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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/577,266	05/23/2000	William G. Johnson	601-1-057N	4282

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EXAMINER	
MORAN, MARJORIE A	

ART UNIT	PAPER NUMBER
1631	18

DATE MAILED: 10/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/577,266	JOHNSON ET AL.	
	Examiner	Art Unit	
	Marjorie A. Moran	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 June 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-21,24-27 and 29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-21,24-27 and 29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

All rejections and objections not reiterated below are hereby withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Claims 19-21, 24-27 and 29 are pending.

Claim Rejections - 35 USC § 103

Claims 19-21, 24 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over CHRISTENSON et al. (Am. J. Med. Genetics (5/1/19990 vol. 84 (2), pp. 151-157) in view of STEEN et al. (Prenatal Diagnosis (1998) vol. 18, pp. 545-555).

Applicant's arguments with respect to claims 19-21 have been considered but are moot in view of the new ground(s) of rejection.

Amended claim 19 recites a method of estimating the probability of a pregnant woman to have offspring which develop a developmental disorder comprising collecting a biological sample containing nucleic acids or protein from one or more subjects, analyzing the nucleic acids or proteins to generate a genotype for alleles of two or more genes associated with folate, pyridoxine and/or cobalamin metabolism, adding the resultant dataset(s) from each subject to a reference dataset, formulating a model based on the subject dataset(s), then analyzing the combined dataset by binary logistic regression to determine a predicted probability for the woman to have offspring which develop a developmental disorder and to estimate a genetic and environmental susceptibility of the individual toward having offspring which develop a developmental disorder. Claim 20 limits the model to an added step of adding or subtracting a genetic variable, re-analyzing data, and choosing a model which best fits the data. Claim 21

recites testing the model for goodness of fit. Claims 24 and 29 recite a method of lowering the risk of a woman to have offspring with a developmental disorder or of treating an asymptomatic individual at risk for having an offspring with a developmental disorder, as predicted in the method of claim 21, by administering methylfolate, cobalamin, or pyridoxine to the woman.

CHRISTENSEN teaches a method of estimating the probability of a pregnant woman to have a child with an NTD, as set forth above. CHRISTENSEN teaches measurement of two genetic variables, MTHFR and MTR (Tables I and III), and thus suggests adding the MTR genetic variable to his MTHFR data. AS CHRISTENSEN determines that MTR has little or negative affect on the probability of a woman having a child with an NTD (pp. 154-155), and his subsequent model does not include MTR data (Tables IV and V), CHRISTENSEN suggests "choice" of a model which best fits his data; i.e. one which does not include MTR data. CHRISTENSEN's teaching for confidence intervals and calculation of statistical significance suggest teaching of "testing" his model for goodness of fit. CHRISTENSEN teaches a genotype for alleles of two or more genes, but does not specifically teach including data for two or more genes in his model, nor does CHRISTENSEN specifically teach administration of folate, cobalamin, or pyridoxine.

STEEN teaches that both MTHFR mutation and vitamin B12 deficiency are independent risk factors for neural tube defects (NTD), wherein a correlation between an MTHFR mutation and spina bifida has been established (pp. 546-547), as has a correlation between reduced B12 and NTD (pp. 546 and 549). STEEN also teaches

that ratios of products to substrates of blocked catalytic reactions (such as those involved in methionine synthesis) can be used as genetic determinants for inherited disorders (p. 549), and teaches that the methionine synthase gene has been mapped and sequenced (p. 551). STEEN teaches that a calculation of a ratio of methionine to folate and of methionine to a product of folate and homocysteine from maternal amniotic fluid may be indicative of NTD risk in fetuses of those mothers (pp. 551-552). STEEN concludes that both folate and vitamin B12 supplementation would be helpful in reducing the risk of NTD (p. 552).

It would have been obvious to one of ordinary skill in the art at the time of invention to have included the measurements and ratio calculations of STEEN in the method of CHRISTENSEN, where the motivation would have been to genetically discriminate between women at risk for having children with NTDs by combining independent risk factors, as taught by STEEN. It would further have been obvious to have chosen a model in the method of CHRISTENSEN and STEEN which best fits the data for estimating the odds of a woman having a child with an NTD, as suggested by the teachings of CHRISTENSEN that an MTR polymorphism probably is NOT a marker for the probability of a child having and NTD, and the teaching of STEEN that independent risk factors may be combined to produce a more accurate prediction, and where the motivation would have been to choose a model which most accurately predicts the probability of NTDs, as suggested by the totality of CHRISTENSEN's and STEEN's teachings. In addition, it would have been obvious to have administered folate and/or cobalamin (vitamin B12), as taught by STEEN, to women identified as being at

risk in the method of CHRISTENSEN and STEEN, where the motivation would have been to reduce the risk of NTDs caused by either folate or vitamin B12 deficiency, as taught by STEEN (p. 552).

Claims 24 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over CHRISTENSON et al. (Am. J. Med. Genetics (5/1/19990 vol. 84 (2), pp. 151-157) in view of STEEN et al. (Prenatal Diagnosis (1998) vol. 18, pp. 545-555), as applied to claims 19-21, 24 and 29 above, and further in view of MAGGIO et al. (Current Therapeutic Research (1994) vol. 55 (12), pp. 1471-1476, abstract only).

Claims 24 and 29 (see above) recite a method of lowering the risk of a woman to have offspring with a developmental disorder, as predicted in the method of claim 21, by administering methylfolate, cobalamin, or pyridoxine to the woman.

Applicant's arguments with respect to claims 24 and 29 have been considered but are moot in view of the new ground(s) of rejection. In response to the argument that folic acid and methylfolate are distinct compounds, it is noted that MAGGIO specifically teaches administration of methylfolate in the rejection set forth below.

CHRISTENSEN and STEEN make obvious a method of estimating the probability of a pregnant woman to have a child with an NTD, wherein folate or cobalamin may be administered, as set forth above. CHRISTENSEN specifically teaches monitoring folate, cobalamin and homocysteine concentrations in his method (pp. 154-156), and teaches administration of folic acid to women (p. 151, abstract).

STEEN specifically teaches administering folate and vitamin B12 (cobalamin). Neither CHRISTENSEN nor STEEN specifically teaches that their folate is methylfolate.

MAGGIO teaches that methyltetrahydrofolate is also called methylfolate, and teaches that methylfolate may be administered to patients to prevent folate deficiency.

It would have been obvious to one of ordinary skill in the art at the time of invention to have administered the methylfolate of MAGGIO to women determined to be at risk for having children with NTD's in the method of CHRISTENSEN and STEEN where the motivation would have been to reduce folate deficiency in patients, and where both CHRISTENSEN and STEEN teach that it is desirable to reduce folate deficiency in women at risk for having children with NTDs.

Claims 24 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over CHRISTENSON et al. (Am. J. Med. Genetics (5/1/19990 vol. 84 (2), pp. 151-157) in view of STEEN et al. (Prenatal Diagnosis (1998) vol. 18, pp. 545-555), as applied to claims 19-21, 24, and 29 above, and further in view of SARILL et al. (US 6,274,564, filed 9/17/1997).

Applicant's arguments with respect to claims 24 and 29 have been considered but are moot in view of the new ground(s) of rejection.

Claims 24 and 29 (see above) recite a method of lowering the risk of a woman to have offspring with a developmental disorder, as predicted in the method of claim 21, by administering methylfolate, cobalamin, or pyridoxine to the woman.

CHRISTENSEN and STEEN make obvious a method of estimating the probability of a pregnant woman to have a child with an NTD, wherein folate and cobalamin may be administered, as set forth above. CHRISTENSEN specifically teaches monitoring folate, cobalamin and homocysteine concentrations in his method (pp. 154-156), and teaches administration of folic acid to women (p. 151, abstract). STEEN specifically teaches administration of folate and vitamin B12. Vitamin B12, in some formulations, is cobalamin and in other formulations, is cyanocobalamin. CHRISTENSEN and STEEN do not specifically teach cobalamin.

SARILL teaches periconceptual supplementation with vitamin B12 (which he calls cyanocobalamin) or cobalamin to prevent or decrease the incidence of neural tube defects (col. 7, lines 23-43).

It would have been obvious to one of ordinary skill in the art at the time of invention to have administered the vitamin B12 or cobalamin of SARILL to women determined to be at risk for having children with NTD's in the method of CHRISTENSEN and STEEN where the motivation would have been to administer a compound known to reduce the incidence of NTD's, as taught by both STEEN and SARILL.

Claims 25-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over CHRISTENSON et al. (Am. J. Med. Genetics (5/1/19990 vol. 84 (2), pp. 151-157) in view of STEEN et al. (Prenatal Diagnosis (1998) vol. 18, pp. 545-555), as applied to claims 19-21, 24, and 29 above, and further in view of SCHOLL (IDS ref: Am. J. Clin. Nutrition (1996) vol. 63, pp. 520-525).

Applicant's arguments with respect to claims 25-27 have been considered but are moot in view of the new ground(s) of rejection.

Claim 25 recites a method of determining of a treatment is advisable for a woman at risk for having offspring with a developmental disorder, as predicted in the method of claim 21, by measuring the concentration of a risk factor from a tissue sample or body fluid of the pregnant woman and determining that treatment is advisable when the concentration of risk factor is above or below an accepted range. Claim 26 recites a method of monitoring the effect of administering methylfolate, cobalamin or pyridoxine to the woman of claim 25. Claim 27 limits the risk factor of claims 25 and 26 to be homocysteine, folate, or cobalamin.

CHRISTENSEN and STEEN make obvious a method of estimating the probability of a pregnant woman to have a child with an NTD, as set forth above. CHRISTENSEN specifically teaches measurement of folate, cobalamin and homocysteine concentrations in his method (pp. 154-156), as set forth above. STEEN teaches administration of folate and cobalamin, and teaches measurement of folate, cobalamin, and homocysteine (p. 548). CHRISTENSEN further teaches that mothers with low RBC folate (in the lowest quartile) are at risk for having children with NTD's (Fig. 1), thus suggesting that those with folate concentrations below an accepted range be treated. CHRISTENSEN and STEEN do not teach monitoring the effect of treatment with folate, cobalamin or pyridoxine.

SCHOLL teaches monitoring the effect of administering folate to pregnant women (abstract), teaches that periconceptual use of folate is known to reduce

incidence of NTD's (p. 520), and teaches that low folate levels are associated with low birth weight and preterm delivery (Tables 2, 3, 4).

It would have been obvious to one of ordinary skill in the art at the time of invention to have monitored the folate levels of pregnant women, as taught by SCHOLL, in the method of CHRISTENSEN and STEEN where the motivation would have been to ensure adequate levels of folate to reduce/prevent a host of teratogenic/prenatal complications, including development of NTD's, low birth weight and preterm delivery, as taught by all of CHRISTENSEN, STEEN and SCHOLL.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marjorie A. Moran whose telephone number is (703) 305-2363. The examiner can normally be reached on Monday to Friday, 7:30 am to 4 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on (703) 308-4028. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 305-3524.

MARJORIE MORAN
PATENT EXAMINER

Marjorie A. Moran

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